The Examiner states that, on a basis of this Reference L disclosure, it would have been obvious to one skilled in the art to employ "an adamantane compound" to treat Alzheimer's disease.

Reconsideration and withdrawal of this ground of rejection is respectfully solicited.

A careful inspection of the Reference L disclosure shows that the adamantyl group is hardly considered in the reference to be anything like a critical substituent in the complex compounds suggested by the reference for the treatment of Alzheimer's disease or Alzheimer dementia. As a matter of fact, the adamantyl group is said to be just one of many possible "alkyl groups" having one to ten carbon atoms, which might be present in the amino end group B, where it would appear as R^4 in the substituent of the formula $-NHR^4$, or which might be present as an R^1 substituent in the amino group on the aspartic acid moiety as one of many possible "alkyl" substituents having one to eighteen carbon atoms. There is absolutely nothing in the reference which indicates that the adamantyl group has anything to do with the effectiveness of the compounds claimed in Reference L to be useful in the treatment of Alzheimer's disease or Alzheimer dementia. The only thing that can be said from the reference is that it teaches that the presence of one or more adamantyl groups in a highly-complicated peptide derivative does not appear to interfere with the activity of the extremely complex compounds there claimed for their intended uses. And, of course, there is absolutely no suggestion whatever in Reference L that <u>any</u> adamantane group or compound <u>by itself</u> (and certainly not applicants' specific adamantane compounds) would have <u>any</u> value for the purposes set forth in the reference, and certainly there is no suggestion that any adamantyl compound by

itself, without being attached to the highly-complex peptide molecule of the reference, would have any activity or use other than such as are or were already known for adamantyl compounds of applicants' type, such as the types of activities and uses set forth on page 4 of the present Specification. To derive anything more than that from the Reference L would be to employ improper hindsight reasoning in making out an untenable rejection based, not upon the disclosure of the reference, but upon the teaching of the present applicants in their own present application.

To conclude otherwise, based upon the reference itself, would go far beyond any rational and logical conclusion, as will be apparent to the Examiner upon reconsideration.

In looking once more at Reference L, adamantyl is therein mentioned only along with numerous other alkyl end groups and substituents, which may perhaps modify the effect of the vasopressin-derivatives of the reference, as identified by the authors of Reference L on page 1 thereof, but the alkyl moieties and in particular the adamantyl moieties are not claimed to be essential for the activity of the Reference L peptides and, in fact, they are shown not to be essential for the activities of the Reference L compounds by virtue of the fact that they are included in a "shotgun" disclosure along with so many other straight or branched chain "alkyl" substituents, all of which groups are also permissible substituents and which may be present instead of the adamantyl substituent or substituents. Accordingly, there is nothing at all essential about the adamantyl group in the compounds of Reference L, and Reference L does not in fact suggest that the adamantyl group is in the slightest responsible for any activity disclosed by Reference L.

The Examiner is surely aware of the fact that one must scientifically discriminate between the pharmacophore (which is the active principle) and appended moieties which may only determine or influence, among other things, the pharmacokinetics of the drug involved.

In the present case, it is clear from Reference L that the adamantyl group is nothing more than an appendant moiety which has little or nothing to do with the effectiveness of the product, as found by the authors of Reference L.

A simple example illustrates the applicants' point dramatically. Clofibrate is the ethyl ester of clofibric acid. Clofibric acid is the lipid-lowering principle. For kinetic reasons, clofibric acid is administered as the ethyl ester. However, no one would expect or believe that ethanol, which is in such case the appendant moiety, is a lipid-lowering agent, just because it is present in the clofibrate molecule and bound therein in the ester form. Indeed, ethanol actually induces an increase of triglycerides, as is well known to all researchers and others who are familiar with lipid-lowering therapy and with models used to induce hypertriglyceridemia in animals.

The Examiner will also surely recognize that this is the case with the adamantyl "merely appendant" moieties in the extremely complex peptide derivatives of the cited Reference L, for which reason the present applicants' employment of their specified adamantyl compounds for their specified activities and uses, which do not involve a peptide derivative or a complex molecule such as present in Reference L, is indeed not only novel, but valuable, and totally unpredictable from anything shown or suggested by the cited Reference L except possibly by the employment of ex post facto

reasoning involving the present applicants' own disclosure which, of course, cannot be used against them and which would therefore be an untenable manner of making out a rejection and improper procedure, as will immediately be apparent to the Examiner.

Accordingly, entry of the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

Appreciation is hereby extended the Examiner for providing a clear, concise, and readily-understandable, as well as highly-constructive, Office Action. Appreciation is also extended to the Examiner for the further search which turned up the cited Reference L, so that it could be disposed of properly on the record.

The undersigned attorney has made an earnest effort to place this application into condition for immediate allowance, as will be apparent to the Examiner. If the undersigned attorney can be of further assistance to the Examiner in the elimination of any possibly-existing insignificant impediment to an immediate allowance of this application, the Examiner is respectfully invited to call the undersigned attorney at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

G O R D O N W. H U E S C H E N

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